Remarks

Amendments to the Claims

Claim 78 is amended to recite a method of generating an immune response in a subject a subject. The specification supports this amendment at page 13, second paragraph: "In a further aspect, the present invention includes compositions for generating an immunological response, where the composition typically comprises at least one of the expression cassettes of the present invention . . . ."

New claims 98-103 are supported at page 12, lines 10-13: "The native and synthetic polynucleotide sequences encoding the HIV polypeptides of the present invention typically have at least about 85%, preferably about 90%, more preferably about 95%, and most preferably about 98% sequence identity to the sequences taught herein."

The amendments do not add new matter.

Amendments to the Specification

The specification is amended to incorporate by reference a substitute sequence listing, to insert sequence identifiers,[1] and to reformat names of genes and proteins. None of these amendments adds new matter.

Substitute Sequence Listing

A substitute sequence listing accompanies this paper. The substitute sequence listing differs from the sequence listing filed July 23, 2007 in that it includes new SEQ ID NOS:148-

[1] Sequence identifiers were added to Table 4 on page 107 by the amendment filed July 23, 2007.

150, which were present in the specification as filed. The substitute sequence listing does not add new matter.

Objection to Drawings

A replacement Figure 105 accompanies this paper. Please withdraw the objection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

Claims 38 and 78-90 stand rejected under 35 U.S.C. § 112 ¶ 1 as lacking written description. Applicants respectfully traverse the rejection.

The written description rejection is based on the Office Action's allegation that the specification does not indicate Applicants' possession of nucleotide sequences having at least 90% percent identity to the full-length sequence of the nucleotide sequence SEQ ID NO:120 and encoding immunogenic Env polypeptides. To advance prosecution, claim 38 is amended to delete the recitation "immunogenic." Example 11 of the Written Description Training Materials (Rev. 1. March 25, 2008) illustrates why claim 38, as amended, satisfies the written description requirement. Claim 1 of Example 11 recites an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid homology sequence identity to SEQ ID NO:2. The Training Materials explain that this claim is adequately described despite the fact that it encompasses a vast genus of nucleic acids and a lack of any teaching about which 15% of the amino acids can vary. Description is adequate because the knowledge in the art regarding the genetic code would put one in possession of the genus of nucleic acids; because one could list all of the claimed nucleic acids with the aid of a computer, and because synthesis and sequencing of nucleic acids were routine.

The same analysis applies to claim 38 as amended. One would be put in possession of the claimed genus of nucleic acids using the knowledge in the art; one could determine all possible sequences using a computer, and conventional sequencing and synthesis techniques were used routinely to generate and identify nucleic acids. The skilled artisan would therefore have recognized that Applicants were in possession of the subject matter of amended claim 38 at the time of filing. Claims 78-90 depend from claim 38 and are thus adequately described. The arguments above apply with equal force to new claims 98-103.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 38 and 78-90 Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claim 38 stands rejected under 35 U.S.C. § 112 ¶ 1 as not enabled. The Patent Office asserts that unreasonable experimentation would be required to practice the invention in view of the large number of sequence variants and the difficulty of predicting which variants would be immunogenic. To advance prosecution, applicants have amended claim 38 to remove the recitation of "immunogenic"; thus, this aspect of the enablement rejection is no longer relevant with respect to claim 38 or to new claims 98-100.

Claims 78-90 also are rejected as not enabled. On page 12, the Office Action contends that use of the term "immunize" requires that the "immune response of interest must be prophylactic or therapeutic." To advance prosecution, claim 78 is amended to recite a method of generating an immune response by introducing an expression cassette. As amended, the claims no longer recite language that allegedly requires a prophylactic or therapeutic response.

The claims are fully enabled with regard to stimulating an immune response. The enablement requirement of 35 U.S.C. § 112, first paragraph states that a patent specification must

teach a person skilled in the relevant art how to make and use the invention claimed. Whether a specification enables a claimed invention is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). The proper standard for determining whether the present specification meets the enablement requirement for claim 78 is whether any experimentation which may be needed to identify sequences within its scope is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). A skilled artisan would not require undue experimentation in order to identify such sequences.

The Patent Office calculates that the scope of the claim 78 encompasses an enormous number of possible sequences and gives the impression that a skilled artisan would have floundered in a vacuum of confusion. This is not the case, however. First, Applicants note that the number calculated by the Patent Office includes variants of the sequence that would introduce a stop codon and result in premature termination of the polypeptide. A skilled artisan would recognize that it would be absurd to generate sequences that immediately terminate.

Second, many of the mutations in the nucleotide sequence would be silent; that is, the amino acid sequence would not change. Thus, the large number cited by the Patent Office is merely a collection of the statistical possibilities and not a relevant measure of sequences that a skilled artisan would consider.

Third, by the December 31, 1998 priority date of the present application, a variety of methods were available to those of skill in the art to identify epitopes. These methods include empirical methods such as use of PEPSCAN,[2] or by using various approaches techniques to

[2] Geysen *et al.*, *Proc. Natl. Acad. Sci. USA 81*, 3998-4002, 1984; Carter, *Methods Mol. Biol.* 36:207-23, 1994.

predict the location of epitopes, such as use of the Jameson-Wolf antigenic index,[3] neural networks,[4] OptiMer & EpiMer,[5] ADEPT,[6] Tsites,[7] hydrophilicity,[8] antigenic index,[9] or the methods disclosed in Davenport *et al. Immunogenetics* 42:392-97, 1995. Indeed, the EpiMer program was designed specifically to identify suitable T cell epitopes for HIV vaccines. Once likely epitopes are identified, it is merely a matter of routine screening to determine which epitopes are immunogenic and therefore useful in the method of claims 78-90. Creation of the peptides identified by these programs and determination of their ability to stimulate an immune response may be time-consuming and expensive, but it is a routine practice in the art. The test for whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The skilled artisan could readily use software programs such as those cited above to narrow the choices of sequences to those likely to be immunogenic before performing actual experiments to determine the immunogenicity of various Env polypeptides. The amount of experimentation to practice the full scope of the claim is not trivial, but it is not so great or complex as to meet the standard for unreasonable experimentation.

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[3] Jameson *et al. CABIOS* 4(1):1818-86, 1988.

[4] Brusic *et al., Bioinformatics* 14(2):121-30, 1998.

[5] Meister *et al., Vaccine* 13(6):581-91, 1995; Roberts *et al., AIDS Res. Hum. Retroviruses* 12(7):593-610, 1996.

[6] Maksyutov & Zagrebelnaya, *Comput. Appl. Biosci.* 9(3):291-97, 1993.

[7] Feller & de la Cruz, *Nature* 349(6311):720-21, 1991.

[8] Hopp, *Peptide Research* 6:183-90, 1993.

[9] Welling *et al., FEBS Lett.* 188:215-18, 1985.

The Office is required to consider the factual evidence in the record which weighs in favor of enablement. *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996). In this case, the level of guidance in the art at the time of filing in basic structural biochemistry, immunology and, more specifically, HIV-related immunology and structural biology, was such that the skilled artisan had broad and detailed knowledge of amino acids of Env polypeptides that could and could not be changed without destroying immunogenicity. The skilled artisan would therefore have been able to identify amino acid sequences within the scope of the claim that would retain an immunogenic function and, by virtue of the genetic code, nucleotide sequences that encode the amino acid sequences.

These arguments apply with equal force to new claims 101-103. Please withdraw the rejection.

Respectfully submitted,

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By: _____

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